Stadtman Tenure-Track Search, Computational Biology Committee

Place: Natcher Balcony B
Time: 8:30 AM - 12:30 PM on
Date: Monday, December 13

From 1:30 - 5:00 group interviews and individual interviews will be held.
If interested in meeting with a candidate, please contact
Artie Sherman, asherman@nih.gov, 301-496-4325

8:30 - 8:55 Christopher Maher, University of Michigan
"*Discovery of Novel Gene Fusions in Prostate Cancer Using Next Generation Transcriptome Sequencing*"

9:05 - 9:30 Fan Wu, Medical College of Wisconsin
"*Multiple-Scale Modeling of Energy Metabolism in Heart Failure and Brain Cancer: Targeting at Efficient Metabolic Therapies*"

9:40 - 10:05 Zhiyong Lu, National Library of Medicine, NIH
"*Mining Literature for Accelerating Knowledge Acquisition and Discovery*"

10:15 - 10:45 Break

10:45 - 11:10 Fangqiang Zhu, NIDDK, NIH
"*Multiscale Simulations of Ion Channel Gating*"

11:20 - 11:45 Jin Liu, NCI, NIH
"Allosteric Regulation: The Ubiquitin System and Beyond"

11:55 - 12:20 Christopher Snow, California Institute of Technology
"*Bespoke Computational Models for Structure Prediction and Design within a Protein Family*"

ABSTRACTS

1. Christopher Maher

Discovery of Novel Gene Fusions in Prostate Cancer Using Next Generation Transcriptome Sequencing

Characterization of gene fusions in cancer has led to the identification of several successful therapeutic targets, as exemplified by the small molecule inhibitor Gleevec targeting BCR-ABL1 in chronic myeloid leukemia. Given the high prevalence of fusions involving the oncogenic ETS family transcription factors in prostate cancer (~60-70%), we hypothesize that the remaining portion of prostate cancer patients are also likely to harbor "driver" gene fusions. Therefore, this work focuses on employing Next Generation transcriptome sequencing technologies to detect "driver" gene fusions that are hidden by non-specific aberrations in the remaining ~30% of prostate cancer patients lacking any detectable ETS gene fusion. To accomplish this we first developed an integrative approach, which leverages both the Illumina and 454 sequencing platforms, to detect chimeric transcripts. This led to the discovery of a recurrent, prostate-specific, androgen inducible RNA chimera, SLC45A3-ELK4. However, given the rapid advances in sequencing technologies, we have adopted a paired-end chimera nomination strategy for elucidating novel gene fusions. This talk will focus on the bioinformatic approaches for leveraging the high-throughput, unbiased view of prostate cancer transcriptomes offered by NGS to systematically detect novel transcriptional aberrations that would have eluded microarray based approaches. Overall, these approaches led to the discovery of a novel class of gene fusions associated with more aggressive forms of prostate cancer. These findings are of major clinical impact as this class of gene fusions not only define a novel prostate cancer subtype for stratifying patients, but can serve as valuable therapeutic targets.

2. Fan Wu

Multiple-Scale Modeling of Energy Metabolism in Heart Failure and Brain Cancer – Targeting at Efficient Metabolic Therapies

Complex human diseases, such as heart failure and brain cancer, are often associated with impaired regulation of metabolism and consequently altered metabolic states. By targeting at metabolism at a systems level, metabolic therapies have exhibited potentials in treating heart failure and brain cancer. Due to inherent complexity of metabolic networks, mechanistic computational modeling is required to delineate underlying regulatory mechanisms and to develop efficient metabolic therapies. Our previously developed multiple-scale computational model of heart energy metabolism has been applied to explain experimentally observed phenomena on cardiac energetics in heart failure. We have shown that fine balances between key metabolic pools (including total adenine nucleotide pool, creatine pool, and total exchangeable phosphate pool) are maintained in both normal and failing hearts to preserve the cardiac energetic state. The model simulation further suggests that an efficient metabolic therapy for heart failure requires simultaneous restoration of the three key metabolic pools in a proper manner. In my future research plan, I propose to develop a multiple-scale mechanistic computational model of brain metabolism in healthy and cancerous brain tissue. The brain metabolism model will be developed at different functional levels, by following our previous methodology in modeling cardiac energetics. The proposed computational model will provide a powerful tool in understanding fundamental phenomena in brain metabolism on a systems level, and in seeking optimal settings of metabolic therapies that exploit reduced metabolic flexibility of cancerous brain cells.

3. Zhiyong Lu

Mining Literature for Accelerating Knowledge Acquisition and Discovery

The explosion of biomedical information in the past decade or so has created new opportunities for discoveries to improve the treatment and prevention of human diseases. But the large body of knowledge—mostly captured as free text in journal articles—and the interdisciplinary nature of biomedical research also present a grand new challenge: how can scientists and health care professionals find and assimilate all the publications relevant to their research and practice? In response, my research is set to improve the way the scientific community access the biomedical literature using various text mining techniques, with a focus on real-world applications in PubMed. In this talk, I will first present a large-scale characterization of PubMed user's search needs and habits, which allowed us to identify the challenging areas in PubMed search and retrievals. My talk will focus on two of those issues: one involves generating query suggestions for enabling users to make more focused search and the other recognizing named entities (e.g. disease) for presenting users with multiple related resources. I will present the automatic methods we have developed for these two tasks, and further demonstrate how they are applied in the PubMed context. Our recent usage analysis shows that these new features are being heavily used by millions of PubMed users on a regular basis. My future research will continue on improving literature access as well as on challenging tasks in text mining such as automatic entity and relation identification from free text.

5. Jin Liu

Allosteric Regulation: The Ubiquitin System and Beyond

The ubiquitin system regulates protein degradation. It is a central cellular machine, involved in many cellular processes, and linked to diseases such as cancer and AIDS. A key step in the ubiquitination pathway involves ubiquitin transfer from the E2 conjugating enzyme to the substrate. Yet, crystallography illustrated that the distance to be bridged in the catalytic reaction is on the order of tens of Angstroms, raising the question of how this distance is bridged and the ubiquitin transfer regulated. We discovered that the ubiquitination mechanism is multiply allosterically-controlled. Our molecular dynamics simulations combined with available experimental data led us to propose a 'two-arm machine' model, as an answer to one of the long-standing mechanistic questions related to Cullin-RING E3 ubiquitin ligases. Based on this model, we developed a novel strategy to identify allosteric sites to target E3 ligases in disease. This strategy was successfully used to design rescue mutants against the VHL disease, and was validated by experimental evidence. Our results point to a new paradigm in E3 drug discovery: currently efforts aim at the active sites of these proteins; our results suggest allosteric ones. Allosteric drugs are advantageous: they are highly selective and are expected to lessen side effects which often arise because of binding site conservation. In my future research, I propose to further explore the complex allosteric mechanism of the ubiquitination which involves multiple steps, protein factors and post-translational modification events; to collaborate with experimentalists to identify allosteric drug sites in E3 ligases; and to develop combined multi-scale tools and strategies for allosteric drug design. I plan to seek other important and challenging biological systems. I hope that eventually these efforts together with experimental data will unveil mechanisms, provide unconventional tools and strategies, and a prototype for allosteric drug discovery.

6. Christopher Snow

Bespoke Computational Models for Structure Prediction and Design within a Protein Family

Nature recombines proteins to create new sequences with desirable properties. We emulate this mechanism in the laboratory to study protein biophysics and to engineer enhanced enzymes. Structure-guided recombination of homologous proteins generates diverse sequences which still have a high probability of retaining the parental fold and function. For example, we have constructed a synthetic family of cytochrome P450 heme domains wherein the average "chimera" differs from the nearest natural "parent" sequence by 72 mutations. Critically, by assaying a small fraction of this library we have trained a simple 1-body model to accurately predict experimental thermostability values for the remaining family members. Following the same strategy we have (i) recombined three natural parent genes coding for fungal class II cellobiohydrolases and (ii) trained a predictive computational model for the stability of the resulting synthetic cellulases.
Recombination is also a powerful method for searching protein conformational space. Fragments of known PDB structures are key building blocks for protein structure prediction algorithms. For example, ab initio Rosetta folding relies on fragment insertion Monte Carlo. Unfortunately, Rosetta and other existing protein conformational search algorithms are sampling limited. Structure refinement calculations (with and without experimental data) would benefit from improved sampling of nearby protein conformations. Therefore, we have developed an approximation that radically increases sampling speed given a discrete conformational search space.